REMARKS/ARGUMENTS

Applicant provides herewith an amendment to the claims as described above. Support for amendments to the claims is discussed elsewhere below. Applicant submits that no new matter has been added by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Office Action dated August 22, 2005, included objections to the claims and rejections based on alleged indefiniteness (35 U.S.C. §112, second paragraph), alleged anticipation (35 U.S.C. §102) and alleged obviousness (35 U.S.C. §103). Applicant traverses all objections and rejections to the extent that they may be applied to the amended claims, for the reasons noted herein. The present Response with Amendment is fully responsive to each of the Examiner's points, and Applicants respectfully request reconsideration of the claims in view of the amendments and remarks herein.

THE STATUS OF THE CLAIMS

Claims 1-50 are pending with entry of this amendment. Claims 5 and 47 are amended herein. This amendment to the claims introduces no new matter. Support for the amendment is found in the specification as originally filed. These amendments are made without prejudice and are not to be construed as abandonment of any subject matter subject matter or agreement with any objection or rejection of record.

OBJECTIONS TO THE SPECIFICATION AND CLAIMS

In the present Office Action dated August 22, 2005, the Examiner objected to the claims for allegedly being in improper dependent form. Specifically, the Examiner states that the claim 47 broadens the claim on which it depends (*i.e.*, on claim 45). Without prejudice, Applicant has amended claim 47. The currently amended claim 47 now depends from claim 44 (not claim 45). In view of this amendment, Applicant respectfully requests that this objection be withdrawn.

35 U.S.C. §112, SECOND PARAGRAPH

In the present Office Action dated August 22, 2005, the Examiner has rejected claims 1-50 under 35 U.S.C. §112, second paragraph as indefinite. The Examiner states that various

steps in the method of claim 1 are unclear, and asks for clarification by pointing to appropriate sections in the specification for support. Applicants point out that the claim language cited by the Examiner does not appear in the independent claim 25, and so these grounds for rejection can not be used to reject claim 25. Applicants believe that the Examiner intended to reject claims 1-24 and 26-50 under 35 U.S.C. §112, second paragraph.

The Examiner states that claim 1, step (a) "contacting a plurality of biological samples with a plurality of members of a compound library" is unclear, and asks for clarification. Specifically, the Examiner states that it is unclear whether each biological sample is being contacted with a single member of the compound library, or with a plurality of members of the compound library.

As described in the specification, the invention provides methods for compound library screening, where a plurality of biological samples are contacted with members of a compound library, and the physiological effects of contacting the biological samples with the library constituents are assessed. In some embodiments, each biological sample is treated with one single member of the compound library. See, *e.g.*, the specification at page 6, line 19 , where each sample "has been treated with (or contacted with or exposed to) a member of a compound library." See also, page 18, lines 27-28, where it is stated "Typically, biological samples, such as samples of a cell line in culture, are exposed to, or treated, e.g., contacted, with a member of a chemical or compound library." And also at page 18, lines 30-33, "Typically, a large number of expressed RNA samples derived from biological samples, for example, a large number of samples each corresponding to a population of the same cell line, each of which has been treated with a different member of the compound library, are spatially arrayed . . . "

However, it is not intended that the methods of the invention be limited to biological samples being treated with one single member from a compound library. Indeed, a biological sample can be treated with a plurality or subset of constituents from a compound library. For example, this is described in the specification at page 19, lines 2-14, where biological samples can be exposed to one or more members of a library, e.g., chemical or biochemical constituents.

In a second instance, the Examiner states that claim 1, step (c) "arraying a plurality of nucleic acids corresponding to the plurality of expressed RNA samples to produce a nucleic acid array" is unclear, and asks for clarification. The Examiner provides two interpretations of this method step, neither of which is entirely accurate. Applicants provide clarification below.

As described in the specification, the invention provides methods for compound library screening, where a plurality of biological samples are contacted with members of a compound library, and the physiological effects of contacting the biological samples with the library constituents are assayed. In these methods, an RNA sample (or amplified nucleic acid products there from, *e.g.*, cDNA) from each biological sample (typically corresponding to treatments from different members of a compound library) is obtained. Each RNA sample will contain a multitude of expression products, since the sample will typically be representative of the entire cellular RNA pool or mRNA pool. A plurality of RNA samples is then used to construct an array, typically where each RNA sample is assigned to a unique spatial location on a solid substrate, e.g., a glass slide. Thus, a single nucleic acid array comprises a plurality of RNA samples, which in turn each comprise a plurality of expressed RNA species.

Support for these methods is found throughout the application. With regard to the arrangement and construction of the nucleic acid arrays as recited in step (c) of claim 1, see, *e.g.*, page 6, lines 16-27; page 10, lines 8-13; and Example 1 at paragraph 0190. This array configuration is also depicted in FIG. 1 (see paragraph 0073) and FIG. 4 (see paragraph 0077).

In the present Office Action, the Examiner has rejected claim 1 under 35 U.S.C. §112, second paragraph as indefinite for omitting essential steps resulting in a gap between the steps. The Examiner states, "it appears that the sample from which the plurality of defined sequence probes must be treated with a candidate compound and its expression level compared with a control hybridization signal in order to detect whether the candidate compound produces a physiological effect. However, the step of producing/isolating a plurality of defined sequence probes from a sample treated with a candidate compound is missing."

Applicant respectfully disagrees, and traverses this rejection. Applicants believe that the Examiner has misunderstood the methods of the invention, especially with regard to the origin of the defined sequence probes. Applicants provide clarification below.

The invention provides methods for screening a compound library. In these methods, a plurality of RNA samples are obtained from a plurality of biological samples (typically corresponding to treatments from different members of a compound library). The collection of RNA samples is then used to construct an array, typically where each RNA sample is assigned to a unique spatial location on a solid support. Thus, a single nucleic acid array comprises a plurality of RNA samples, which in turn each comprise a plurality of expressed RNA species. These arrays are then probed with defined sequence probes in order to observe differences in gene expression patterns in the various RNA samples. The defined sequence probes that are used are not particularly limited, and can correspond in sequence to any gene of interest. Contrary to the Examiner's statement, the defined sequence probes are not produced or isolated from the RNA samples. The defined sequence probes can be produced by any desired method for DNA probe synthesis. See the definition of "synthetic probe" at paragraph 0051. See also, *e.g.*, paragraphs 0011, 0073 (especially lines 28-30 and FIG. 1), 0137 and 0138.

Thus, defined sequence probes are amply described in the specification. A description of the origin or synthesis of the defined sequence probes is not a necessary step in the method of claim 1. There is no gap in the method steps of claim 1, as each step in the method follows logically from the previous step. Applicants request withdrawal of this rejection.

In the present Office Action, the Examiner has rejected claim 5 under 35 U.S.C. §112, second paragraph as indefinite for insufficient antecedent basis for "the control biological sample." Applicant has amended claim 5 to correct a clerical error in the dependency of this claim. The currently amended claim 5 now depends from claim 3 (not claim 1), thereby correcting the antecedent basis of the phrase. In view of this amendment, Applicants request that this rejection be withdrawn.

35 U.S.C. §102

In the Office Action dated August 22, 2005, claims 25-27, 33, 34, 37-45 and 50 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Dooley *et al.*, U.S. Patent No. 6,635,423. The rejection applies to the multiple dependent claims as they depend from claim 25. Applicant respectfully disagrees, and traverses this rejection.

In order for a reference to anticipate a claim, the reference must teach each and every element of the claim (MPEP 2131). Dooley *et al.*, does not meet this requirement. As previously discussed in the Response dated May 12, 2005, the Examiner has overlooked critical defining features of the invention. These novel features of the invention are specifically recited in the independent claim 25. Because Dooley *et al.* does not teach these limitations, neither claim 25 nor any claim that depends from claim 25 can be anticipated by Dooley *et al.*

The invention provides inverted microarray configurations

Claim 25 of the present application recites a method for simultaneously quantitating a plurality of expression products from a plurality of biological samples, where the methods use *arrayed amplified products* (*i.e.*, attached to a substrate) that have been derived from biological sample RNA. The arrays are hybridized with a plurality of defined sequence probes where each probe is uniquely labeled, and the resulting hybridization complexes are then detected. Applicant believes that the Examiner has mischaracterized Dooley *et al.* in comparison to the present invention.

Microarrays of the present invention use an "inverted" configuration. This approach is emphasized throughout the specification, and is most clearly described in paragraphs 0036-0038 and 0216-0218. Step (a) of claim 25 provides a nucleic acid array comprising a plurality of amplified nucleic acids corresponding to a plurality of expressed RNA samples, each obtained from a biological sample. Thus, the nucleic acid array of the present invention has amplified sample material immobilized onto the array. Step (b) of claim 25 provides a hybridizing step where the sample arrays are hybridized with a plurality of soluble phase defined sequence probes, which are each uniquely labeled.

Dooley *et al.* describe classical microarray configurations

Dooley *et al.* describes nucleic acid microarrays that utilize the classical microarray configuration. The classical configuration, as described in the specification at paragraph 0008, typically involve the arrangement of finite numbers of ***defined*** sequence ("bait") nucleic acid molecules attached to and spatially arrayed on a solid phase surface, each in a unique addressable location. This array is then typically hybridized to a labeled cDNA pool derived from cellular RNA samples (which commonly comprise a small number of amplified RNA species).

The "informative nucleic acid arrays" described by Dooley *et al.* are in the classical microarray format, *not* an inverted array format. Dooley *et al.* provides arrays of selected defined sequences (the unlabeled "bait" sequences) that are potentially complementary to differentially expressed genes. These arrays of defined sequences are hybridized with labeled cDNAs prepared from RNA samples collected from biological samples. These steps are clearly outlined in Figure 1 of Dooley *et al.* (see steps II and IV). Thus, the defined or known nucleic acid sequences are attached to the array substrate.

The "informative arrays" of Dooley *et al.* are merely classical arrays that contain smaller subsets of the thousands of immobilized gene sequences typically arrayed onto a classical microarray. Figure 1 in Dooley *et al.* describes the construction and use of the informative array.

In that Figure, step II describes the use of the classical microarray configuration, where the arrays contain thousands of immobilized genes. These classical arrays are hybridized with soluble phase pools of cDNA that were derived from biological sample RNA. These cDNA pools are termed "probes" because the cDNA pool is labeled (e.g., with a radioisotope, fluorescent label, etc.). The resulting hybridization complexes are then visualized. Steps III and IV describe the process of making the informative array. Essentially, genes are identified from the first nucleic acid array experiment that have biological significance, (e.g., genes that are differentially expressed, signature biomarkers and sentinel biomarkers). Differentially expressed genes can include genes that are unregulated or downregulated in response to a treatment or exposure to a compound. An informative nucleic acid array is simply a classical microarray that contains arrays of

immobilized sequences complementary to the biologically significant genes. These informative microarrays are used in hybridization reactions with RNA samples in the same way that a classical microarray is used in hybridization reaction with an RNA sample (see step V).

The present invention is distinct from Dooley *et al.*

It appears that the Examiner is equating the informative nucleic acid arrays of Dooley *et al.* with the methods of the present invention (including claim 25). This is simply not correct. Dooley *et al.* does not teach a nucleic acid array prepared from amplified nucleic acid samples derived from a plurality of expressed RNA samples (claim 25, step a). The sample-derived nucleic acid samples in Dooley *et al.* are in the soluble phase, while the nucleic acid samples of the present invention are in the solid phase attached to the array.

Furthermore, Dooley *et al.* does not teach a hybridizing step using defined sequence probes where each probe is capable of generating a different detectable signal, and where the defined sequence probes are in the soluble phase (claim 25, step b). *The defined sequence elements in Dooley et al. are unlabeled, while the defined sequence elements of the present invention are labeled.*

Since Dooley *et al.* fails to teach each element of the claimed invention (as recited in independent claim 25), Dooley *et al.* does not anticipate claim 25.

"Probes" as used in Dooley *et al.* do not equate with "probes" as used in the present invention

Applicant notes that some confusion may arise because of the different uses of the term "probe" in the present application and in Dooley *et al.* In both cases, the probe refers to the molecule (or collection of molecules) that comprise a detectable moiety. However, in these two cases, the probes are very different types of molecules. In Dooley *et al.*, the probe is the uncharacterized heterogeneous pool of labeled cDNA derived from the biological RNA sample. See Figure 1, part II, in Dooley *et al.* In contrast, the probes in the present specification are the labeled defined sequence nucleic acid molecules that are used to interrogate the biological sample nucleic acids that are affixed to the array. In the present

invention, a plurality of defined sequence probes are used in a single hybridization reaction, where each probe has a unique label.

The Examiner also pointed to additional subject matter in Dooley *et al.* that allegedly further rendered dependent claims 26, 27, 33, 34, 37-45 and 50 (as they depend from claim 25) anticipated. If an independent claim is novel, so must each claim that depends upon the independent claim also be novel, as each dependent claim contains all of the limitations found in the independent claim. The Examiner's pointing to additional support in Dooley *et al.* for alleged anticipation of the dependent claims is insufficient to render any of those dependent claims anticipated. Because Dooley *et al.* do not teach each element of the claimed invention, Applicant requests that this rejection be withdrawn.

35 U.S.C. §103(a)

In the present Office Action dated August 22, 2005, the Examiner makes new rejections of the claims under 35 U.S.C. §103(a) as allegedly obvious and unpatentable over:

i) Dooley *et al.*, U.S. Patent No. 6,635,423, in view of International Publication WO 97/10365 to Lockhart *et al.*;

ii) Dooley *et al.*, in view of Lockhart *et al.*, and further in view of Cho *et al.*, *Proc. Natl. Acad. Sci. USA* 98(17):9819-9823 (August 14, 2001); and,

iii) Dooley *et al.*, in view of Lockhart *et al.*, and further in view of Nilsen *et al.*, U.S. Patent No. 6,046,038, and Shuber, U.S. Patent No. 5,882,856.

Dooley *et al.* (alone or in combination with Lockhart *et al.*) is deficient

Claims 1-13, 15-24, 26, 27, 30-45 and 47-50 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Dooley *et al.*, in view of Lockhart *et al.* The rejection of these claims, including the multiple dependent claims, was based on their dependency on claim 1. Applicants disagree, and traverse the rejection.

A *prima facie* case of obviousness requires that the prior art reference(s) must teach all of the limitations of the claims. The combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention (M.P.E.P § 2142-2143). Contrary to the Examiner's statements, Dooley *et al.*, Lockhart *et al.* or any combination of features there from fail this test.

Claim 1 is drawn to screening methods using an array with a plurality of nucleic acids corresponding to expressed RNA derived from biological samples. As discussed extensively above, and in the Response filed on May 12, 2005, Applicants have described the salient features of the invention. That is, the claimed invention uses a non-traditional microarray configuration, where the normal sample/probe relationship is inverted. In this novel configuration, a plurality of nucleic acid samples corresponding to a plurality of expressed RNA samples is affixed onto an array (e.g., a solid phase support surface) (claim 1, step c). This array is then probed (*i.e.*, used in a hybridization reaction) with a plurality of soluble phase nucleic acid probes of defined sequence, where each probe comprises a distinct label (claim 1, step d). This novel approach is emphasized throughout the specification, and is most clearly described in paragraphs 0036-0038 and 0216-0218.

The features of Dooley *et al.* cited by the Examiner do not equate with the steps of claim 1.

Applicants note that the Examiner appears to rely solely on the teachings of Dooley *et al.* to formulate this 35 U.S.C. §103(a) rejection of claim 1. Because the Examiner does not appear to rely on any feature from Lockhart *et al.* or any other art in addition to Dooley *et al.*, the statutory basis for the rejection of claim 1 under 35 U.S.C. §103(a) is unclear.

Dooley et al. is discussed extensively above. In a situation analogous to the Dooley *et al.* 102(e) rejection described above, the salient, defining feature of the claimed invention, namely, the use of an inverted microarray format, have been overlooked. An inverted microarray format is not taught anywhere Dooley *et al.* or Lockhart *et al.*, or by any combination thereof.

The Examiner alleges that Dooley *et al.* discloses a method of screening a candidate library that comprises all the steps of claim 1 of the present invention (see the Office Action at page 10). The Examiner is incorrect.

Claim 1, step (c) reads: "arraying a plurality of nucleic acids corresponding to the plurality of expressed RNA samples to produce a nucleic acid array." The Examiner points to the following support in Dooley *et al.* that allegedly teaches this step. Applicant addresses each citation below.

Column 10, line 8: Examiner may be pointing to the "subsequent experiments" feature that results in "informative nucleic acid arrays." This section does not describe the construction of an array where the material arrayed onto the solid support is uncharacterized material derived from a plurality of RNA samples or derivative products. The construction of the informative nucleic acid array of Dooley *et al.* uses known individual selected gene sequences that have been deemed of interest, and do not correspond to expressed RNA samples (as required in claim 1, step c).

Column 3, lines 36-38: This section describes informative arrays and states "placing sequences derived from ranked differentially expressed genes on the informative array. The gene may be expressed in the biological process." The present invention does not employ ranked differentially expressed gene sequences as bait on an array. This section in Dooley *et al.* does not describe a plurality of RNA samples (or material derived directly from the RNA samples, e.g., cDNA samples) assembled on an array, as required in claim 1, step c.

Column 5, lines 17-19: This section describes step IV of Figure 1, where the informative nucleic acid arrays of Dooley *et al.* are designed and constructed. These arrays use only informative and relevant gene sequences to construct the array. This section of Dooley et al., does not describe using a plurality of RNA samples (or material derived directly from the RNA samples, e.g., cDNA samples) to produce an array.

Claim 1, step (d) reads: "hybridizing a plurality of defined sequence probes, which probes each comprise a different polynucleotide sequence, and which probes are each capable of generating a different detectable signal, to the nucleic acid array." The Examiner points to the following support in Dooley *et al.* that allegedly teaches this step:

Column 10, line 7-9: This section cited by the Examiner states "the same gene sequences may be used in subsequent experiments to find other compounds that produce a similar sentinel biomarker response." This describes the construction of the informative arrays of Dooley *et al.* The informative arrays use labeled sample material in the soluble phase, and furthermore, the samples are uniformly labeled with a single detection means. See Figure 1, step II-2 in Dooley *et al.* This passage does not teach the hybridization of a plurality of defined sequence probes (that are in the soluble phase) with an array comprising affixed RNA sample material, and further, where each defined sequence probe has a different

label that permits detection distinct from each of the other defined sequence probes (as required in claim 1, step d).

Applicant submits that the paragraphs cited in the Office Action (as noted above) do not teach or disclose the methods of the invention.

Lockhart *et al.* does not remedy the shortcomings of Dooley *et al.*

Dooley *et al.* is deficient with regard to teaching each limitation of the claim 1. For example, as described above, Dooley *et al.* is silent with regard to steps (c) and (d) in claim 1. Lockhart *et al.* describes gene expression monitoring using high density oligonucleotide arrays. The methodologies described in that publication are classical array configurations (see, Figure 1 in Lockhart *et al.*). Even if the teachings of Dooley *et al.* are combined with Lockhart *et al.*, the combination remains defective in rendering claim 1 obvious. Dooley *et al.* does not teach an inverted array configuration, as required in claim 1 of the present invention; Lockhart *et al.* does not remedy this defect. Applicant submits that the rejection is improper and respectfully requests that the rejection of claim 1 be withdrawn.

Applicant notes that the Examiner appears to makes a statement that admits to the deficiencies in Dooley *et al.* (see the Office Action dated August 22, 2005 at page 12, lines 12 through 15). That quote from the Examiner states, "Dooley et al. do not employ their method for contacting a plurality of samples with a plurality of members of a compound library and generating an RNA sample from each of the plurality of the biological sample and arraying a plurality of nucleic acids corresponding to the plurality of expressed RNA samples to produce an array."

The Examiner also rejected claims that are dependent on claim 1, citing supplemental support for these rejections in either Dooley *et al.*, Lockhart *et al.* or the likely motivation of one of ordinarily skill in the art. On this basis, the Examiner rejected claims 2-13, 15-24, 26, 27, 30-45 and 47-50 as they depend on claim 1. Because claims 2-13, 15-24, 26, 27, 30-45 and 47-50 are dependent on claim 1, they contain all of the limitations of claim 1. As argued above, claim 1 is non-obvious, and it follows that claims that are dependent on claim 1 must also be non-obvious. In view of this, the Examiner has not made a *prima facie* case for

obviousness for any claim that is dependent on claim 1, and the Applicant requests that the rejection of claims 2-13, 15-24, 26, 27, 30-45 and 47-50 be withdrawn.

"Informative arrays" of Dooley *et al.* are not "inverted arrays" of the present invention

On pages 15-17 of the Office Action dated August 22, 2005, the Examiner acknowledges the Applicant's argument that the present invention utilizes a novel microarray configuration that flips the standard microarray paradigm, where the microarrays of the invention have the nucleic acid samples fixed to the solid support, and where the defined sequence probes are in the soluble phase and are used to interrogate the sample arrays. The Examiner states that this point is not persuasive for various reasons. The Examiner states that arrays of the invention are disclosed by the use of "informative arrays" as described in Dooley *et al.*

Applicant strongly disagrees. The Examiner has mischaracterized the informative arrays of Dooley *et al.* The Examiner fails to recognize the fact that "informative arrays" are classical arrays that merely contain smaller subsets of the thousands of immobilized gene sequences that are typically arrayed onto a classical microarray. Figure 1 in Dooley *et al.* describes the process for building informative arrays. Step II describes the use of the classical microarray configuration, where the arrays contain thousands of immobilized genes. These classical arrays are hybridized with soluble phase pools of cDNA that were derived from biological sample RNA. These cDNA pools are termed "probes" because the cDNA pool is labeled (e.g., with a radioisotope, fluorescent label, etc.). The resulting hybridization complexes are visualized after a wash step. See, steps II-1 through II-4.

Information obtained from steps II and III is used to construct the informative array. Essentially, genes are identified in steps II and III that have biological significance, (*e.g.*, genes that are differentially expressed, signature biomarkers or sentinel biomarkers). Differentially expressed genes can include genes that are unregulated or downregulated in response to a treatment or exposure to a compound. These differentially expressed genes are used to make the informative array, as described in step IV.

An informative nucleic acid array is simply a classical microarray that contains arrays of immobilized sequences complementary to the biologically significant genes. These informative microarrays are used in hybridization reactions with RNA samples in the same way that a classical microarray is used in hybridization reaction with an RNA sample (see step V).

It appears that the Examiner is equating the informative nucleic acid arrays of Dooley *et al.* with the inverted microarrays of the present invention (see the Office Action on pages 16-17). This is simply not correct, for the many reasons provided in this Response and in the Response filed on May 12, 2005.

Cho *et al.* does not remedy deficiencies in the combination of Dooley *et al.* and Lockhart *et al.* The dependent claims stand.

Claim 14 was rejected under 35 U.S.C. §103(a) as allegedly obvious over Dooley *et al.*, in view of Lockhart *et al.*, and further in view of Cho *et al.*, *Proc. Natl. Acad. Sci. USA* 98(17):9819-9823 (August 14, 2001). Applicant disagrees, and traverses the rejection.

Cho *et al.* describe a mammalian cell experimental system where the host cells are exposed to antisense oligonucleotide treatments. Cho *et al.* observe global changes in gene expression patterns resulting from these treatments by using microarray methodologies. The Examiner attempts to combine the teachings of Dooley *et al.* with Lockhart *et al.*, and further with Cho *et al.* to arrive at the method of claim 14. This attempt fails. Applicant points out that the Examiner has again erroneously equated the informative nucleic acid array strategy of Dooley et al. with the nucleic acid arrays of the present invention.

The Examiner's argument presupposes that Dooley *et al.* (with or without the combination of Lockhart *et al.*) renders claim 1 as obvious. Claim 14 is ultimately dependent on claim 1, and thereby contains all of the limitations of claim 1. As discussed in the sections above, the combination of Dooley *et al.* with Lockhart *et al.* is deficient and incapable of rendering claim 1 as obvious. Thus, if claim 1 is non-obvious, so too must claim 14 be non-obvious. The addition of Cho *et al.* to the combination does nothing to impact that conclusion. The Examiner has not made a *prima facie* case for obviousness, and Applicant requests that this rejection be withdrawn.

Nilsen *et al.* and Shuber do not remedy deficiencies in the combination of Dooley *et al.*and Lockhart *et al.* Claims that are dependent on claim 1 stand.

Claims 28, 29 and 46 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Dooley *et al.*, U.S. Patent No. 6,635,423, in view of Lockhart *et al.*, International Publication WO 97/10365, and further in view of Nilsen *et al.*, U.S. Patent No. 6,046,038, filed August 12, 1997, issued April 4, 2000, and Shuber, U.S. Patent No. 5,882,856, issued March 16, 1999. This rejection was based on the dependency of the multiple dependent claims on claim **1**. Applicant disagrees with the Examiner's finding, and traverses the rejection.

Nilsen *et al.* describe DNA dendrimer probes that can be used for probe signal amplification. Shuber describes the use of multiplex PCR amplification and the use of universal priming sequences in PCR. The Examiner attempts to combine the teachings of Dooley *et al.* with Lockhart *et al.*, and further with Shuber to arrive at the method of claims 28 and 29 as they depend from claim 1; and combine Dooley *et al.* with Lockhart *et al.*, and further with Nilsen *et al.* to arrive at the method of claim 46 as it depends from claim 1. This attempt fails.

The Examiner's argument presupposes that Dooley *et al.* (with or without the combination of Lockhart *et al.*) renders claim **1** as obvious. Claims 28, 29 and 46 are ultimately dependent on claim 1, and thereby contain all of the limitations of claim 1. As discussed in the sections above, the combination of Dooley *et al.* with Lockhart *et al.* is deficient and incapable of rendering claim 1 as obvious. Thus, if claim 1 is non-obvious, so too must dependent claims 28, 29 and 46 also be non-obvious. The addition of Nilsen *et al.* or Shuber to the combination does not alter that conclusion. The Examiner has not made a *prima facie* case for obviousness, and Applicant requests that this rejection be withdrawn.

Nilsen *et al.* and Shuber do not remedy deficiencies in the combination of Dooley *et al.*and Lockhart *et al.* Claims that are dependent on claim 25 stand.

Claims 28-32, 35-36 and 46-49 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Dooley *et al.*, U.S. Patent No. 6,635,423, in view of Lockhart *et al.*,

International Publication WO 97/10365, Nilsen *et al.*, U.S. Patent No. 6,046,038, filed August 12, 1997, issued April 4, 2000, and Shuber, U.S. Patent No. 5,882,856, issued March 16, 1999. These multiple dependent claims were rejected based on their dependency on claim 25. Applicants disagree with the Examiner's assessment, and traverse the rejection.

Dooley *et al.*, Lockhart *et al.*, Nilsen *et al.* and Shuber are all discussed above. The Examiner again attempts to combine the teachings of Dooley *et al.*, Lockhart *et al.*, Nilsen *et al.* and Shuber to arrive at the methods of claims 28-32, 35-36 and 46-49 as they depend from claim 25. The Examiner provides supplemental support for the rejection of these dependent claims by pointing to the locations of support in Lockhart *et al.*, Nilsen *et al.* and Shuber for the various dependent limitations, and also in view of the level of ordinary skill in the art (Office Action, pages 22-24). However, the Examiner's approach in making these rejections is unsuccessful.

The Examiner's argument presupposes that Dooley *et al.* (with or without the combination of Lockhart *et al.*) renders claim 25 as obvious. Claims 28-32, 35-36 and 46-49 are ultimately dependent on claim 25, and thereby contain all of the limitations of claim 25. As discussed thoroughly in the rejection under section 35 U.S.C. §102(e) above, Dooley *et al.* is deficient and incapable of rendering claim 25 as anticipated. Furthermore, this deficiency of Dooley *et al.* can not be overcome by the addition of Lockhart *et al.*, Nilsen *et al.* or Shuber (in any combination) to render claim 25 obvious. These references do not teach, for example, an array comprising nucleic acids corresponding to a plurality of expressed RNA samples (claim 25, step a); and do not teach the use of a plurality of soluble phase defined sequence probes each comprising a different detectable signal (claim 25, step b).

Thus, if claim 25 is non-obvious, so too must claims 28-32, 35-36 and 46-49 also be non-obvious. The addition of Nilsen *et al.* or Shuber to the combination does nothing to impact that conclusion. The Examiner has not made a *prima facie* case for obviousness, and Applicant requests that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this application are definite, novel and non-obvious, and are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

In the Office Action dated August 22, 2005, the Examiner acknowledged the Applicant's request for an telephone interview. As per the Examiner's request, Applicant includes herewith form PTOL-413A to request an interview. Applicants respectfully request an interview prior to the Examiner taking action on the present Response and Amendment.

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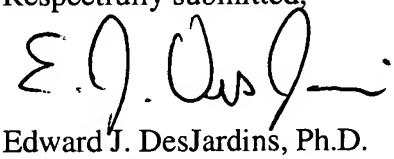
Respectfully submitted,



Edward J. DesJardins, Ph.D.
Reg. No: 51,162

Attachments:

1) a transmittal sheet;
2) petition for one month extension;
3) form PTOL-413A; and
4) a receipt acknowledgement postcard.